Patient Perceptions of Stool-Based DNA Testing for Colorectal Cancer Screening

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Purpose: Stool-based DNA (SB-DNA) testing is an emerging colorectal cancer screening strategy that offers a convenient, noninvasive, and potentially more acceptable alternative to existing screening tests. The objectives of this study were to compare patient perceptions of SB-DNA testing, fecal occult blood testing (FOBT), and colonoscopy, and elicit screening preferences.

Methods: A prospective survey was conducted between August 2001 and March 2003 of asymptomatic, mostly average-risk subjects aged ≥50 years who were participating in a multicenter comparison of SB-DNA testing and FOBT for detecting colorectal neoplasia. Subjects completed a 25-item questionnaire within 48 hours after undergoing a colonoscopy, which served as the standard. Respondents were asked to rate each of the three screening tests on various prep- and test-related features, using a five-point ordinal scale or yes/no format, and to select a preferred strategy.

Results: A total of 4042 subjects completed the survey (84% response rate). SB-DNA testing received the same or higher mean ratings than FOBT for most prep- and test-related features. When compared with colonoscopy, SB-DNA testing received higher ratings for all prep- and test-related features except perceived accuracy, where colonoscopy was rated higher. Overall, a higher percentage of patients preferred SB-DNA testing (45%) to both FOBT (32%) and colonoscopy (15%) for routine screening ($p < 0.001$); 8% had no preference.

Conclusions: Patients willing to undergo colonoscopy, SB-DNA testing, and FOBT perceive SB-DNA testing to have a number of advantages over the other two tests. Moreover, many such patients prefer SB-DNA testing to FOBT and colonoscopy for routine screening.
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Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related death and fourth most commonly diagnosed cancer among men and women in the United States.[1] Over the past decade, sufficient evidence has accumulated to suggest that screening is a cost-effective strategy for reducing both CRC incidence and mortality.[2] Consequently, most authoritative groups now endorse screening for both average and high-risk patients.[3–6] Despite a compelling rationale and widespread endorsement by authoritative groups, however, screening rates remain far below those necessary to achieve significant reductions in CRC mortality or incidence.[7,8]

Poor patient adherence has been a major barrier to CRC screening. Previous studies have identified practical reasons (e.g., conflicts with work or family commitments, inconvenience, lack of interest, and cost), lack of current health problems or worrisome symptoms, and most importantly, lack of a physician recommendation as the major reasons for nonparticipation.[9,10] Negative attitudes toward the tests themselves are also prevalent. Fecal occult blood testing (FOBT) is widely perceived as embarrassing or distasteful, whereas concerns about pain, discomfort, and injury are common for sigmoidoscopy and colonoscopy.[9,10] Lack of confidence to complete the tests (i.e., lack of self-efficacy), anxiety about the consequences of screening (e.g., the need for further testing or a cancer diagnosis), and inconsistent or inadequate support from friends, family, media, and insurers are other frequently cited reasons for nonparticipation.[9,10]

Stool-based DNA testing is a novel screening strategy that offers a convenient, noninvasive alternative to existing screening tests. Like FOBT, stool-based DNA testing can potentially detect neoplasia anywhere in the large bowel with sample collection that can be performed at home. Unlike FOBT, however, no dietary or medication restrictions are required and the sample can be collected using a specialized device that obviates the need for

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handling stool. Published studies to date suggest that stool-based DNA testing with a commercially available multitarget assay—which detects 21 point mutations in the K-*ras* proto-oncogene or APC and p53 tumor suppressor genes, a microsatellite instability marker (BAT-26), and a marker of defective apoptosis ("long DNA")—has a sensitivity in the range of 62% to 91% for detecting colorectal cancers and 50% to 82% for advanced adenomas; specificity has been in the range of 93% to 100%.[11–14] These data would suggest that the performance of SB-DNA for detecting advanced colorectal neoplasia may be superior to FOBT (sensitivity ~24%; specificity ~94%),[15] but inferior to colonoscopy (sensitivity ~95%; specificity ~100%).[6] An equally important yet undefined issue relates to the question of whether stool-based DNA testing is acceptable to patients. Hence, the principal objective of this study was to assess and compare the perceptions of asymptomatic, mostly average-risk subjects undergoing stool-based DNA testing, FOBT, and colonoscopy as part of one of the large multicenter trials. A secondary objective was to elicit CRC screening preferences.

Methods

Survey Sample

The survey sample population comprised asymptomatic men and women aged ≥50 years who were participating in a multicenter comparison of SB-DNA (PreGen-Plus™, EXACT Sciences Corporation, Marlborough MA) and FOBT (Hemoccult® II, Beckman Coulter, Palo Alto CA) for detecting CRC neoplasia. Subjects were recruited through normal patient referral channels at each of the 84 participating U.S. sites, including 71 community-based practices and 13 academic centers, between August 2001 and March 2003. Newspaper advertising and distribution of pamphlets in doctors' offices were also employed at select study site areas to aid in subject recruitment. At the time of recruitment, patients were informed that the purpose of the study was to compare the sensitivities of SB-DNA and FOBT for detecting colorectal cancer, using colonoscopy as the standard; no additional information regarding individual test features or performance was provided. Patients meeting eligibility criteria were stratified on enrollment into three groups based on age: 50 to 54, 55 to 64, and ≥65 years. The goal was to recruit 250 subjects in the 50-to-54 age group, 750 in the 55-to-64 age group, and 4000 in the ≥65 age group to optimize the likelihood of detecting a sufficient number of cancers (n =35) to satisfy pre-study power determinations. Subjects received monetary honoraria for their participation, which varied in amount from $150 to $250, to cover incidental costs and inconveniences.

Potential subjects presenting with any of the following were deemed ineligible: any prior structural colorectal examination (i.e., colonoscopy, double-contrast barium, "virtual colonoscopy," or flexible sigmoidoscopy) within the past 10 years; personal history of colorectal neoplasia, familial adenomatous polyposis, or hereditary nonpolyposis colorectal cancer or inflammatory bowel disease; personal history of extracolonic cancers other than skin cancer diagnosed within the past 5 years; active gastrointestinal symptoms; two or more first-degree relatives with colorectal cancer; overt gastrointestinal bleeding within the past month; any positive FOBT within the past 6 months; medical conditions for which colonoscopy was contraindicated; anticoagulant use or coagulopathy; and current pregnancy or lactation. Patients at moderate risk because of a family history of colorectal cancer or polyps affecting a single first-degree relative aged ≥50 years were eligible.

Study Design

Consenting subjects were asked to submit a stool sample for SB-DNA testing, prepare three Hemoccult II cards for FOBT, and undergo a colonoscopy within 8 weeks of enrollment. For SB-DNA testing, subjects were instructed to collect a single whole stool using a plastic bucket-type container that could be mounted on the toilet seat and sealed with an airtight lid; samples were shipped directly from home using a courier service within 24 hours of collection. For FOBT, subjects were instructed to implement dietary restrictions specified by the manufacturer and discontinue use of aspirin and other nonsteroidal anti-inflammatory agents for ≥72 hours before collecting two smears from each stool on 3 consecutive days; once completed, the Hemoccult II were returned to the participating site for processing in a prepaid, pre-addressed envelope. Following submission of both the stool sample for SB-DNA testing and Hemoccult II cards for FOBT, subjects underwent colonoscopy after either a Fleet's phosphasoda or balanced-electrolyte, polyethylene-glycol bowel preparation, as recommended by their endoscopist. Apart from procedural instructions, subjects received no specific information regarding the various tests with respect to features such as discomfort, inconvenience, accuracy, or cost.

The study protocol was approved by the institutional review board or ethics committee at each participating site. Informed written consent was obtained from each patient.

Survey Process and Instrument

Subjects were asked to answer a brief questionnaire within 2 days of completing the colonoscopy. The questionnaire was composed of 25 items that asked respondents to rate each of the three screening tests on a variety of features related to the test preparation or test itself, using a five-point ordinal scale or yes/no format. Depending on the feature of interest, questions might relate to all three tests, any two of the three tests, or only a single test. Respondents were also asked to identify a preferred strategy for their "routine" CRC screening. The questionnaire was devoid of all identifiers other than a subject identification number to preserve subject confidentiality. Completed surveys were returned by mail in a prepaid envelope addressed to the contract research organization.

The initial survey instrument was generated in response to feedback from face-to-face interviews and focus groups involving >500 physicians (primary care physicians, gastroenterologists, medical oncologists, and gynecologists) and patients (previously screened and unscreened). The instrument was then reviewed for content validity by a clinical gastroenterologist, pilot tested on 147 patients, and revised before use.

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Table 1. Characteristics of study sample with linked demographic and response data (n = 3359)

Subgroup	n (%)
Gender	
Female	1921 (57.2)
Male	1438 (42.8)
Age (years)	
50–54	164 (4.9)
55–64	491 (14.6)
≥65	2704 (80.5)
Race/ethenicity	
White	3001 (89.3)
Nonwhite	358 (10.7)
Family history	
No	2880 (85.8)
Yes	479 (14.2)
Polyps detected[a]	
No	1772 (53.9)
Yes	1513 (46.1)
Cancer detected[a]	
No	3256 (99.1)
Yes	29 (0.9)

[a]Data missing for 75 subjects (2.2%).

Statistical Analyses

Respondents rated each of the three screening tests on a variety of prep- and test-related features using a five-point ordinal scale, with lower values indicating a more positive rating. To compare ratings, the mean (standard deviation [SD]) rating for each procedure was calculated and compared pairwise through nonparametric signed-rank tests to acknowledge the skewed nature of many of the response distributions (most respondents giving positive ratings). To control for multiple testing, Bonferroni adjustments to pairwise p values were used when reporting significance. Respondents were also asked to give an overall preference to one of the procedures. The percentage of patients preferring stool-based DNA testing, FOBT, or colonoscopy were compared for the overall sample and within subgroups, defined by patient characteristics, through pairwise chi-square goodness-of-fit tests with Bonferroni adjustments to account for multiple testing among the three procedures. Significance for all tests was defined at the two-tailed $p<0.05$ level. All data were analyzed using SAS, version 8 (SAS Institute Inc., Cary NC, 1999).

Results

Response Rate and Respondent Demographics

Eighty-four percent (4042 of 4840) of subjects who completed each of the three screening tests, or 74% of all enrolled subjects, responded to the survey. Demographic data could be directly linked to response data using a subject identification number for 3359 of the 4042 respondents (Table 1). Although these data could not be linked for the other 683 respondents due to the lack of a subject identification number on the first 800 questionnaires distributed, the demographics of those with and without linkage data were nearly identical with respect to gender (chi-square analysis, $p=0.89$); age ($p=0.68$); race/ethnicity ($p=0.66$); family history ($p=0.99$); and findings at colonoscopy (polyps, $p=0.99$; cancer, $p=0.94$). Therefore, the survey data for the entire cohort of respondents ($n=4042$) are presented unless otherwise stated.

Patient Perceptions of Prep- and Test-Related Features

Overall, SB-DNA testing, FOBT, and colonoscopy received highly favorable mean ratings for each of the prep- and test-related features examined. As shown in Table 2, however, SB-DNA testing received higher mean ratings ($p<0.001$) than FOBT for simplicity of the stool sample collection process, comfort, perceived accuracy, and likelihood of repeating the test if recommended by their doctor. In contrast, FOBT received higher mean ratings ($p<0.01$) than SB-DNA testing for perceived prep-related anxiety. SB-DNA testing and FOBT received similar ratings for simplicity of bowel preparation instructions, perceived invasiveness, perceived embarrassment, and test-related anxiety. When compared with colonoscopy, both SB-DNA testing and FOBT received higher ratings ($p<0.001$) for all of the aforementioned prep- and test-related features, except accuracy, where colonoscopy was rated more favorably.

When asked about lost time from work or other activities, only 22.9% of respondents reported lost time due to the prep for colonoscopy and 34.1% due to the test itself, compared to <5% for SB-DNA testing and FOBT ($p<0.001$). The lower-than-expected percentages for colonoscopy presumably reflect the disproportionate number of subjects aged ≥65 years.

Patient Preferences

When asked explicitly which test was preferred for routine screening, 45% of respondents selected SB-DNA testing, 32% FOBT, and 15% colonoscopy ($p<0.001$); only 8% had no preference (Figure 1). Subgroup analyses were performed on the 3103 subjects expressing a preference for whom linkage data were available. The goal was to determine if patient preferences varied on the basis of age, gender, race/ethnicity, family history, or findings at colonoscopy. As shown in Table 3, SB-DNA testing was the preferred screening strategy by both men and women, subjects of all age groups, whites and nonwhites, and those with and without a family history of colorectal cancer. Patients found to have polyps at colonoscopy were significantly more likely to choose SB-DNA ($p<0.01$); in contrast, those found to have cancer were also more likely to prefer SB-DNA testing (40%) than FOBT (32%) or colonoscopy (28%), but differences did not achieve statistical significance ($p>0.05$), possibly because of the small number of subjects with cancer. All subgroups also preferred FOBT to colonoscopy, except patients found to have cancer.

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Table 2. Comparison of overall mean ratings[a] for SB DNA testing, FOBT, and colonoscopy (n=4042)

Question	SB-DNA (SD)	FOBT (SD)	Colonoscopy (SD)	Pairwise differences[b]
1. How easy or difficult to understand were the instructions about preparation for the test?	1.26 (0.56)	1.27 (0.57)	1.33 (0.67)	SB-DNA vs FOBT, NS SB-DNA vs CS, $p = 0.001$ FOBT vs CS, $p = 0.001$
2. How simple or complex was the stool sample collection process?	1.42 (0.71)	1.56 (0.82)	—	SB-DNA vs FOBT, $p < 0.001$
3. How easy or difficult was bowel purging for you?	—	—	2.26 (1.23)	
4. Overall, how comfortable or uncomfortable was the test?	1.39 (0.68)	1.45 (0.72)	1.90 (1.08)	SB-DNA vs FOBT, $p < 0.001$ SB-DNA vs CS, $p < 0.001$ FOBT vs CS, $p < 0.001$
5. How private or invasive did you consider the test to be?	1.26 (0.61)	1.27 (0.62)	2.13 (1.29)	SB-DNA vs FOBT, NS SB-DNA vs CS, $p < 0.001$ FOBT vs CS, $p < 0.001$
6. How embarrassing was it for you to take the test?	1.24 (0.62)	1.22 (0.58)	1.63 (1.00)	SB-DNA vs FOBT, NS SB-DNA vs CS, $p < 0.001$ FOBT vs CS, $p < 0.001$
7. Overall, how much anxiety or nervousness did preparation for the test cause you?	1.39 (0.75)	1.36 (0.72)	2.36 (1.24)	SB-DNA vs FOBT, $p < 0.01$ SB-DNA vs CS, $p < 0.001$ FOBT vs CS, $p < 0.001$
8. Overall, how much anxiety or nervousness did taking the test cause you?	1.33 (0.69)	1.31 (0.66)	2.23 (1.17)	SB-DNA vs FOBT, NS SB-DNA vs CS, $p < 0.001$ FOBT vs CS, $p < 0.001$
9. How accurate or inaccurate do you believe the test to be?	1.72 (0.84)	1.86 (0.93)	1.30 (0.72)	SB-DNA vs FOBT, $p < 0.001$ SB-DNA vs CS, $p < 0.001$ FOBT vs CS, $p < 0.001$
10. If your doctor recommended regular screening using the test, how likely or unlikely would you be to repeat it?	1.33 (0.76)	1.37 (0.80)	1.92 (1.23)	SB-DNA vs FOBT, $p < 0.001$ SB-DNA vs CS, $p < 0.001$ FOBT vs CS, $p < 0.001$

[a]Ratings expressed as mean (SD) using a five-point scale (1 = most favorable; 5 = least favorable).
[b]Bonferroni-adjusted p values for pairwise comparisons via signed-rank test.
CS, colonoscopy; FOBT, fecal occult blood testing; NS, not significant; SB-DNA, stool-based DNA testing; SD, standard deviation.

Discussion

This study found that many patients not only perceive stool-based DNA testing to be an acceptable alternative to both FOBT and colonoscopy, but also prefer stool-based DNA testing over both FOBT and colonoscopy for their routine CRC screening. Nearly half of all respondents selected stool-based DNA testing as their preferred screening strategy compared to about one third for FOBT and only 15% for colonoscopy. Interestingly, this preference for SB-DNA testing did not vary significantly on the basis of age, gender, race/ethnicity, family history, or findings at colonoscopy, with one notable exception: Individuals with colorectal cancers detected at colonoscopy were equally likely to choose any of the three screening modalities. These findings reinforce existing literature suggesting that patients have distinct preferences for screening.[16–18] These findings also suggest that many patients, including those at increased risk because of a positive family history or the presence of polyps or cancer at colonoscopy, prefer a convenient, noninvasive alternative to colonoscopy for their routine screening or surveillance. The extent to which patient knowledge, attitudes, or beliefs about personal susceptibility or disease severity influence these choices is unknown. Nevertheless, these findings have important implications with respect to adherence to serial screening or surveillance, especially since colonoscopy is advocated for those at increased risk by most authoritative groups.[3,4,6]

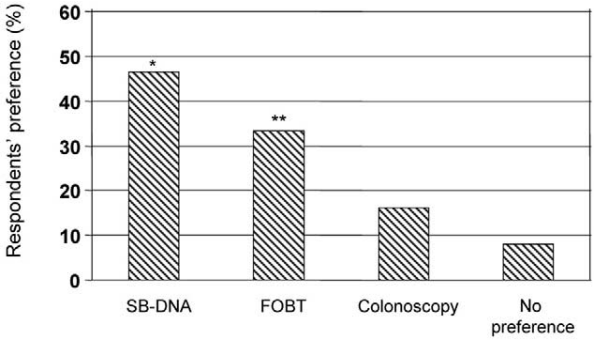

Figure 1. Preferred strategies for routine CRC screening (n =4042). FOBT, fecal occult blood testing; SB-DNA, stool-based DNA testing. *p <0.001, SB-DNA testing versus FOBT and colonoscopy. **p <0.001, FOBT versus colonoscopy.

Conceptually, stool-based DNA testing and FOBT share many similarities from the patient perspective. Both are safe, noninvasive stool-based tests with sample collection performed conveniently at home. Thus, the finding that most patients rated both tests comparably with respect to most prep- and test-related features is

Table 3. Subgroup analyses of respondents expressing preferred strategy for routine colorectal cancer screening (n=3103)

Subgroup	*n*	Prefer SB-DNA (%)	Prefer FOBT (%)	Prefer colonoscopy (%)
Gender				
Female	1768	48.5[a]	33.9[b]	17.5
Male	1335	49.6[a]	36.5[b]	13.9
Age (years)				
50–54	155	59.1[a]	25.3[b]	15.6
55–64	459	53.8[a]	31.6[b]	14.6
≥65	2489	47.7[a]	36.7[b]	15.6
Race/ethnicity				
White	2785	49.9[a]	35.9[a]	14.1
Nonwhite	318	42.5[a]	30.5	27.0
Family history				
No	2667	49.0[a]	35.5[b]	15.5
Yes	436	49.8[a]	34.6[b]	15.6
Polyps detected[c]				
No	1651	49.8[a]	37.4[b]	12.8
Yes				
Cancer detected[c]				
No	3011	49.3[a]	35.4[b]	15.3
Yes	29	40.0	32.0	28.0

[a]$p \leq 0.01$ for SB-BNA vs FOBT and colonoscopy by chi-square goodness of fit.
[b]$p \leq 0.01$ for FOBT vs colonoscopy by chi-square goodness of fit.
[c]Data missing for 63 subjects (2.0%).
CS, colonoscopy; FOBT, fecal occult blood testing; SB-DNA, stool-based DNA testing.

not unexpected. Several noteworthy differences, however, were observed. Stool-based DNA testing received higher ratings for simplicity of the stool collection process and comfort, presumably attributable to the use of a specimen collection container that could be directly mounted onto the toilet seat, thus obviating the need for direct manipulation of stool as required for FOBT. Stool-based DNA testing was also perceived to have superior accuracy, possibly due to its more sophisticated, state-of-the-art technological basis. Importantly, stool-based DNA received more favorable ratings for likelihood of repeating the test if it was recommended by their physician. Conversely, FOBT received more favorable ratings for prep-related anxiety, which is curious since SB-DNA requires no specific preparation or dietary/medication restrictions. Despite their statistical significance, most of these differences were small, and therefore of questionable clinical significance. Nevertheless, extrapolation of these data would suggest that the perceived advantages of stool-based DNA testing supersede its relative disadvantages, thus accounting for the higher percentages of patients preferring stool-based DNA testing over FOBT for their routine screening.

Unlike FOBT and stool-based DNA testing, colonoscopy is a more complicated, risky, and invasive screening option, whose major advantages relate to its superior diagnostic accuracy and therapeutic capacity.[15,19,20] Previous studies have found that patients perceive colonoscopy to be more acceptable than both flexible sigmoidoscopy and double contrast barium.[21,22] This is the first study to directly compare patient perceptions of colonoscopy and stool-based screening tests. Not surprisingly, both stool-based DNA testing and FOBT received superior ratings to colonoscopy for all prep- and test-related features, except accuracy. Perhaps more importantly, both stool-based DNA testing and FOBT were preferred over colonoscopy for routine CRC screening. As previously noted, these findings validate the widespread belief that many patients prefer a convenient, noninvasive, albeit less-accurate screening alternative to colonoscopy for routine testing.

This study has several important strengths that lend credibility to its findings. Its large sample size involving patients from various clinical settings (academic centers, community hospitals, private practices) strengthens both external and internal validity. The high response rate, lack of prior screening experience other than possibly FOBT, and requirement that all respondents undergo all three screening modalities reduced the likelihood of response bias. Moreover, all subjects completed all three tests within a narrow time frame, thus reducing the likelihood of recall bias.

This study also has several important limitations. Its major limitation relates to the issue of patient acceptance. This study explores the perceptions and prefer-

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ences of patients based on their personal experiences with each of the screening tests. Only self-motivated patients willing to complete each of the three screening tests—that is, SB-DNA, FOBT, and colonoscopy—were eligible. Consequently, it remains unknown whether previously unscreened patients operating within an informed or shared decision-making model would express similar preferences if educated about the pros and cons of the various screening modalities based on input from their providers rather than personal experience. More importantly, it remains unknown whether patients who refuse other screening tests would perceive SB-DNA testing to be an acceptable alternative and adhere to a provider's recommendation to undergo screening.

The second major limitation relates to cost issues. Existing evidence clearly demonstrates that patient preferences for CRC screening tests are sensitive to out-of-pocket expenses.[17] Nevertheless, questions related to cost were excluded for two main reasons. First, at the time of survey, cost figures for SB-DNA testing were unavailable. Although perceived to be substantially more than FOBT, it was unclear how it would compare to colonoscopy. Second, it was speculated that SB-DNA testing, if deemed cost-effective, would ultimately be covered by many healthcare insurers, thus obviating concerns about cost. Although a recent economic analysis suggests that SB-DNA testing may be less cost-effective than the other currently recommended screening strategies,[23] improvements in sensitivity and heightened demand would have a favorable impact on cost-effectiveness.

The third limitation involves potential response bias related to the fact that the study was industry sponsored, and that subjects received compensation for their participation. The extent to which theses factors influenced subject responses is impossible to ascertain. Nevertheless, the large number of respondents, the fact that the survey was self-administered at home and returned by mail without subject identifiers other than subject numbers, and the disclaimer in the informed consent document that the sponsor was blinded to the response data help reduce concerns about the impact of this bias on results.

In conclusion, this study finds that many asymptomatic, average and moderate risk individuals not only perceive stool-based DNA testing to have a number of advantages over both FOBT and colonoscopy, but more importantly, prefer stool-based DNA testing to these other modalities for their routine CRC screening. These findings suggest that stool-based DNA testing may be an acceptable alternative to other currently recommended strategies and might increase participation rates. Future studies are needed to validate this speculation, and determine the extent to which stool-based DNA testing truly promotes patient acceptance and adherence to screening recommendations, particularly among individuals who might otherwise refuse screening.

What This Study Adds . . .

Poor patient acceptance is a major barrier to effective colorectal cancer screening.

Stool-based DNA (SB-DNA) testing is a novel screening strategy that offers a convenient, noninvasive, and potentially more acceptable alternative to existing screening tests.

This study is the first to assess and compare patient perceptions of stool-based DNA testing, fecal occult blood testing and colonoscopy.

We found that SB-DNA testing is not only acceptable but also preferred by many for routine screening.

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